CASE OF THE WEEK

PROFESSOR YASSER METWALLY

CLINICAL PICTURE

CLINICAL PICTURE:

A 40 years old female patient presented clinically with a history of common migraine. Clinical examination was free.

RADIOLOGICAL FINDINGS

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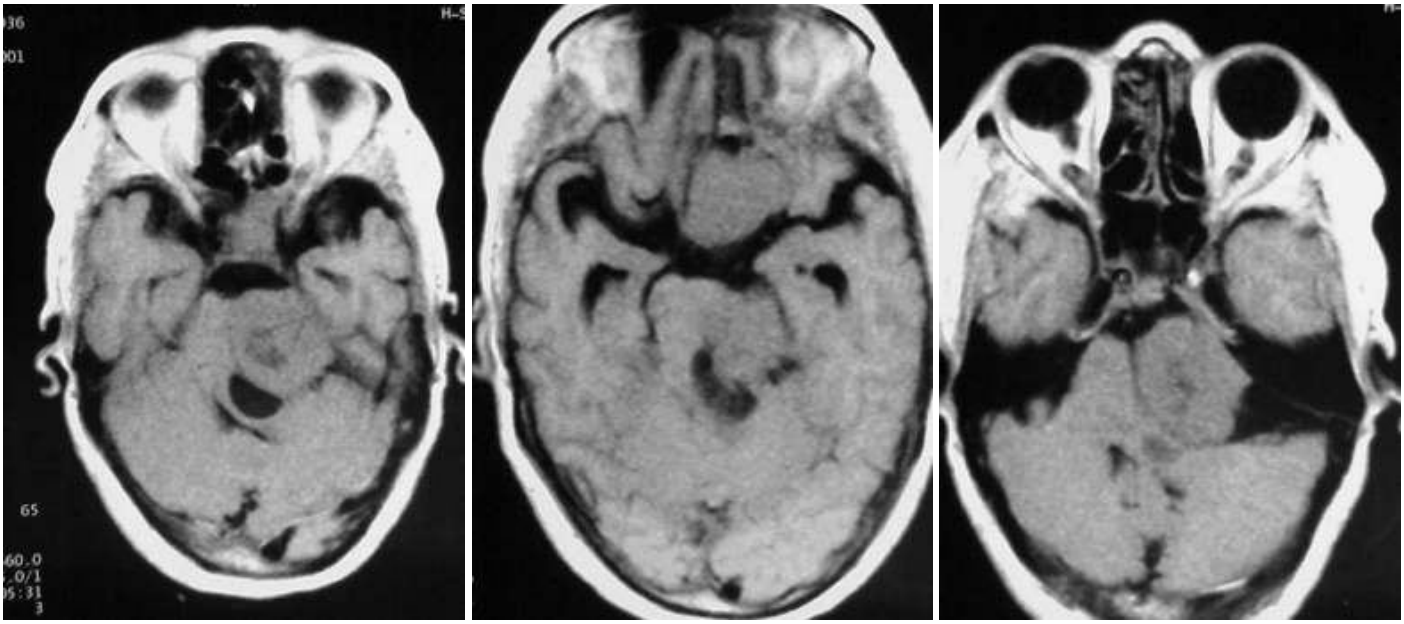

Figure 1. Two syncytial meningiomas. Precontrast MRI T1 images showing two lobulated space occupying lesions in the parasellar/subfrontal and the cerebellopontine regions. The lesions are surrounded by a CSF cleft and a large cyst is seen in the cerebellopontine lesion. Both lesions are isointense to slightly hypointense relative to normal brain tissues. The 4TH ventricle is compressed and pushed posteriorly and to the right. A large arachnoid cyst is seen along the right posterior pole of the cerebellopontine angle mass.

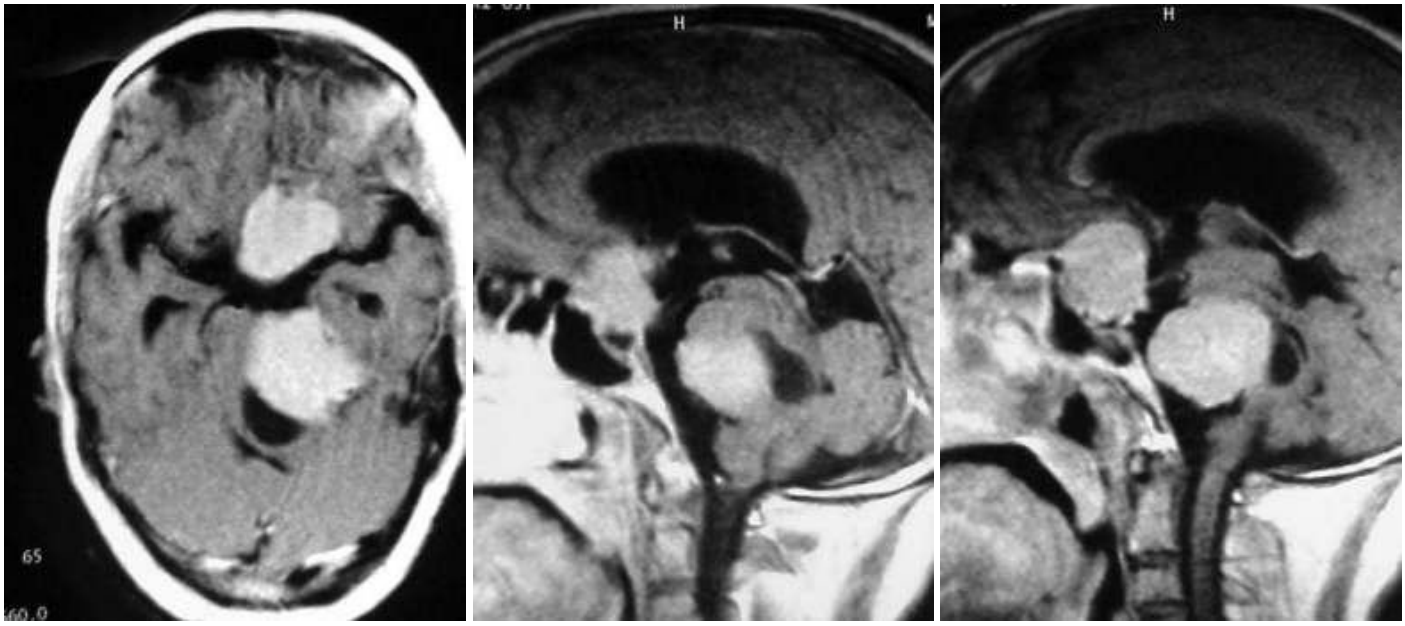

Figure 2. **Two syncytial meningiomas. Postcontrast MRI T1 images. The two lesions showed dense and uniform contrast enhancement. Notice the meningeal tail extending from the subfrontal mass. Also notice the arachnoid cyst. Hydrocephalic changes are also seen.**

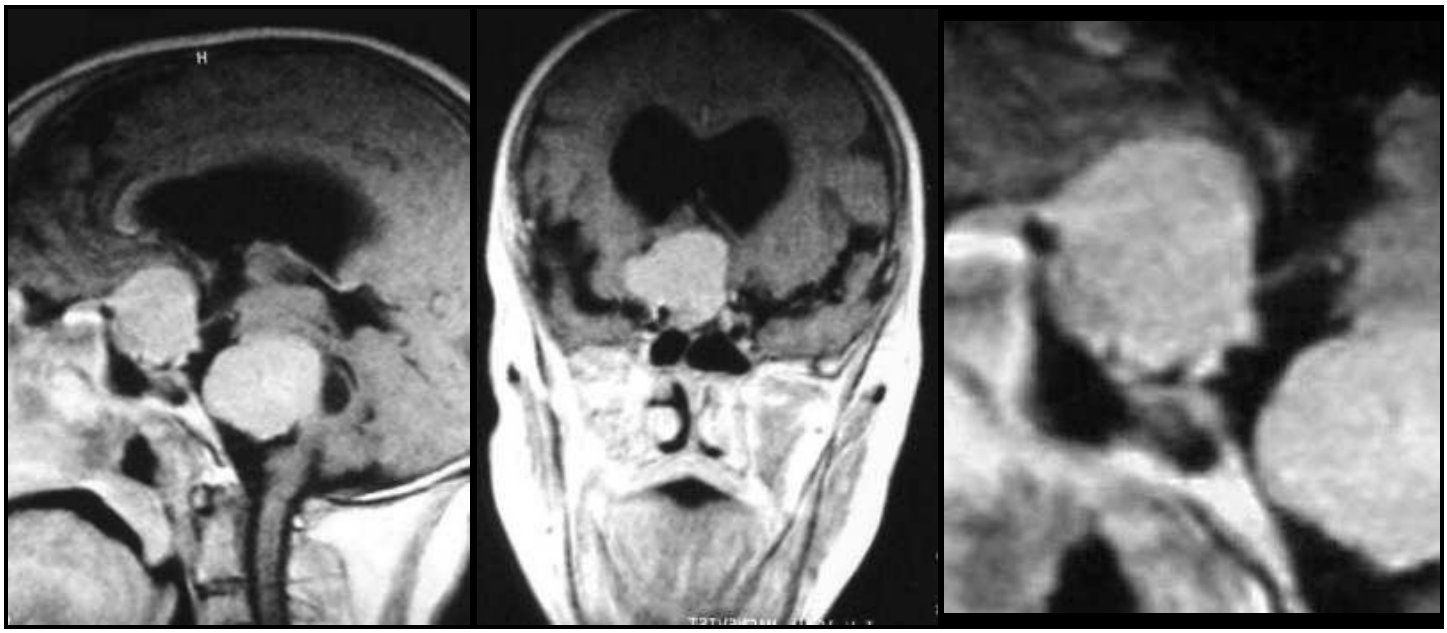

Figure 3. **Two syncytial meningiomas. Postcontrast MRI T1 images. The two lesions showed dense and uniform contrast enhancement. Notice the meningeal tail extending from the subfrontal mass (A,C). Also notice the arachnoid cyst. Hydrocephalic changes are also seen.**

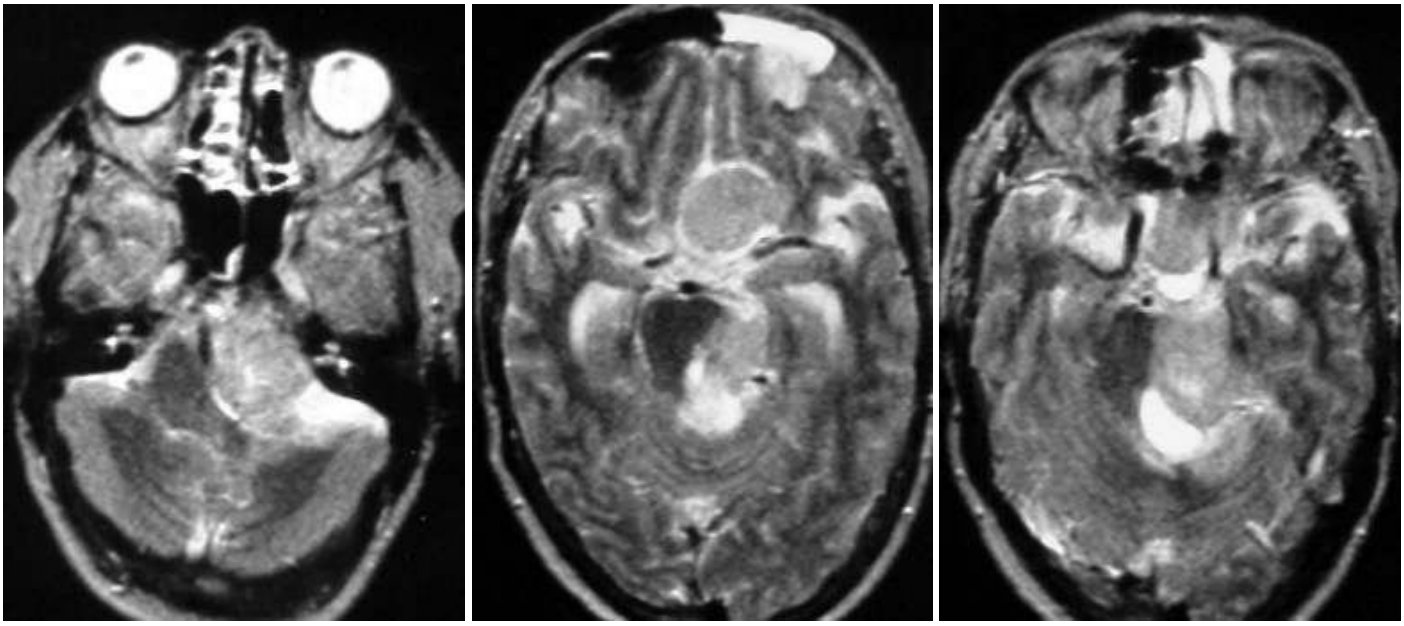

Figure 4. **Two syncytial meningiomas. MRI T2 images. The two lesions are hyperintense on the MRI T2 images. and a large cyst is seen in the cerebellopontine angle mass. Both masses are surrounded by a CSF cleft. Notice the arachnoid cyst along the posterior pole of the cerebellopontine angle mass.**

Table 1. **MRI appearance of the various types of meningiomas**

Type	Comment
Fibroblastic meningiomas	Fibroblastic meningiomas are composed of large, narrow spindle cells. The distinct feature is the presence of abundant reticulum and collagen fibers between individual cells. On MR imaging, fibroblastic meningiomas with cells embedded in a dense collagenous matrix appear as low signal intensity in Tl-weighted and T2-weighted pulse sequences.
Transitional meningiomas	Transitional meningiomas are characterized by whorl formations in which the cells are wrapped together resembling onion skins. The whorls may degenerate and calcify, becoming psammoma bodies. Marked calcifications can be seen in this histologic type. MR imaging of transitional meningiomas thus also demonstrates low signal intensity on Tl- weighted and T2-weighted images, with the calcifications contributing to the low signal intensity.
Syncytial meningiomas	Syncytial (meningothelial, endotheliomatous) meningiomas contain polygonal cells, poorly defined and arranged in lobules. Syncytial meningiomas composed of sheets of contiguous cells with sparse interstitium might account for higher signal intensity in T2-weighted images. Microcystic changes and nuclear vesicles can also contribute to increased signal intensity.
Angioblastic meningiomas	Angioblastic meningiomas are highly cellular and vascular tumors with a spongy appearance. Increased signal in T2-weighted pulse sequence of these tumors is due to high cellularity with increase in water content of tumor.

Thus based on the correlation between histology and MR imaging appearance of meningiomas, it has been concluded that meningiomas significantly hyperintense to cortex tend to be primarily of syncytial or angioblastic type, whereas meningiomas hypointense to cortex tend to be primarily of fibrous or transitional type. Heterogeneous appearance of meningiomas in T2-weighted pulse sequence can be due to tumor vascularity, calcifications, and cystic foci.

Table 2. **MRI characteristics of meningiomas**

Pathological type	T2 MRI appearance
Fibroblastic	Hypointense on the T2 images because of the existence of dense collagen and fibrous tissue
Transitional	Hypointense on the T2 images because of the existence of densely calcified psammoma bodies

Syncytial	**Hyperintense on the T2 images because of the existence of high cell count, microcysts or significant tissue oedema**
Angioblastic	**Same as the syncytial type. Blood vessels appear as signal void convoluted structures**

Table 3. MRI characteristics of meningiomas

MRI feature	Description
Vascular rim	**The peripheries of meningiomas are supplied by branches from the anterior or middle cerebral arteries that encircle the tumour and form the characteristic vascular rim**
Meningeal tail	**The tail extends to a variable degree away from the meningioma site and probably represents a meningeal reaction to the tumour**
Hypointense cleft	**Hypointense cleft between the tumour and the brain that probably represents blood vessels or a CSF interface**

- **The dural tail or "dural flair"**

The dural tail is a curvilinear region of dural enhancement adjacent to the bulky hemispheric tumor. The finding was originally thought to represent dural infiltration by tumor, and resection of all enhancing dura mater was thought to be appropriate. However, later studies helped confirm that most of the linear dural enhancement, especially when it was more than a centimeter away from the tumor bulk, was probably caused by a reactive process. This reactive process includes both vasocongestion and accumulation of interstitial edema, both of which increase the thickness of the dura mater. Because the dural capillaries are "nonneural," they do not form a blood-brain barrier, and, with accumulation of water within the dura mater, contrast material enhancement occurs.

- **Arachnoid cysts**

Acquired arachnoid cysts may develop following surgery, trauma, subarachnoid hemorrhage, neonatal infections and can occasionally occur in association with extra-axial neoplasm. Arachnoid cysts associated with tumors develop as a consequence of CSF loculation surrounded by arachnoid scarring, with expansion of osmotic filtration or via a ball-valve mechanism. These acquired arachnoid cysts have been described variably as acquired secondary or leptomeningeal cysts. The reason arachnoid cysts grow and become space occupying is far from clear. No inner lining is present through which active transport can take place. Neurosurgeons have observed ostia with pulsating fluid in exposed cysts suggesting a hydrodynamic flap-valve or ball-valve mechanism.

DIAGNOSIS:

DIAGNOSIS: MULTIPLE SYNCLINAL MENINGIOMAS (PARASELLAR & SUBFRONTAL AND CEREBELLOPONTINE MENINGIOMAS)

DISCUSSION

DISCUSSION:

The histological appearance of a meningioma is an important predictor of tumor behavior and is frequently a factor in decisions concerning therapy. The relationship between histological features and prognosis is formalized in grading schemes such as those published by the World Health Organization (WHO), most recently in 2007. Although the latest edition is an improvement over previous grading schemes, the WHO scheme still fails to fully address a variety of important issues regarding the relationship between meningioma histological characteristics and behavior. In particular, routine histological examination fails to identify the subset of Grade I tumors that behave aggressively. Because of this, many additional prognostic markers that require immunohistochemical, cytogenetic, or molecular techniques to evaluate are under investigation. Only one, immunohistochemistry for the proliferation marker, Ki 67 (MIB-1), is used routinely and it has only limited utility. It is hoped that an understanding of the genetic changes that underlie tumor progression will improve healthcare professionals' ability to predict the behavior of meningiomas.

Meningiomas are neoplasms derived from arachnoidal (meningothelial) cells. These lesions can occur in people of any

age but commonly present in middle age. Women are more likely to develop a meningioma, with a female/male ratio of approximately 2:1 intracranially and 10:1 in the spine. Most meningiomas are benign ("classic," Grade I), well-circumscribed, slow-growing, and curable by surgery depending on location.[18]

However, some meningiomas are clinically aggressive and can lead to significant complications and even death. Many, but not all, of these aggressive tumors are histological Grade II (atypical) or Grade III (anaplastic or malignant) tumors. As of 2007, the former was reported to account for between 4.7 and 7.2% of meningiomas, whereas the latter comprised 1.0 to 2.8%.[18,30] The authors of some studies have found a larger proportion, approximately 20% of these lesions, to have aggressive histological features.[32] Interestingly, the female predominance in the incidence of meningiomas does not hold for these aggressive tumors.[32]

Two of the most important factors that determine the prognosis in patients with meningiomas are the extent of the resection and the tumor's histological grade. Higher grade meningiomas are more likely not to receive a gross-total resection, and even when they do, there may still be recurrence.[7,29] As an example, the authors of one study found that within 5 years of resection, 12% of benign meningiomas recurred compared with 41% of Grade II tumors.[32] Once a tumor recurs, it is more likely to do so again, ultimately leading to a loss of local control and rarely, metastasis.[5,8,11]

One of the most commonly used classification and grading systems for meningiomas was set forth by the WHO in 2000, and very recently updated in 2007.[18,30] This system summarizes much of what is known about the features seen on routine histological examination that predict aggressive behavior in meningiomas. The 2000 version represented a significant improvement over previous grading schemes and is little changed in the 2007 version. However, some limitations and pitfalls in grading meningiomas remain and will be outlined here.

Because the limits of routine histological examination in predicting tumor behavior have perhaps been reached, a large number of ancillary techniques are under evaluation, including cytogenetics and the use of immunohistochemical markers. So far most of these techniques remain in the literature and have not entered the routine workup for patients with meningiomas. Two exceptions include immunohistochemistry for the proliferation marker Ki 67 (MIB-1) and for PR. Neither of these markers has been incorporated into the 2007 WHO grading scheme for meningiomas, although their significance is cited. Measurement of Ki 67 by immunohistochemistry for the MIB-1 antigen is not uncommonly used as an additional way of evaluating a meningioma's potential for aggressive behavior. Testing for the presence or absence of PRs is used less often but is of special interest because PR antagonists have been used clinically to try to control the growth of meningiomas.

The issue of malignant progression in meningiomas at both the genetic and histological levels is an area of active research. Compelling evidence for progression has been discovered at the genetic level, and the list of genetic alterations associated with different tumor grades continues to expand. A complete discussion of the molecular genetics of meningiomas is beyond the scope of this paper; however, some of the more significant findings will be mentioned.

- **The WHO Classification and Grading of Meningiomas**
  - **Background: The 1993 Version**

In the late 1990s a number of published grading systems for meningiomas were in use. This made it difficult to compare data from different sources. Furthermore, the different grading systems suffered from various weaknesses, including vagueness and subjectivity of criteria.[22]

One of these grading systems was the WHO classification published in 1993.[17] There were two components to this grading system. The first was a scheme by which certain histological features were assessed to decide if meningiomas were the usual Grade I tumors or if they were higher grade. Grade II meningiomas were defined as those "in which several of the following features are evident: frequent mitoses, increased cellularity, small cells with high nucleus/cytoplasm ratios and/or prominent nucleoli, uninterrupted patternless or sheetlike growth, and foci of spontaneous or geographic necrosis." An anaplastic or malignant (Grade III) meningioma exhibited "histological features of frank malignancy far in excess of the abnormalities noted in atypical meningiomas."

  - **Needed Modifications: The Contribution of the Mayo Clinic Studies**

The extreme vagueness and subjectivity of the criteria for atypical and anaplastic meningiomas in this scheme is clear. How many is "frequent"? How much more is "increased"? Exactly how many is "several"? Investigators at the Mayo

Clinic partially addressed these problems by publishing two large studies with two main goals: clarifying the significance of brain invasion and developing objective criteria that would allow reproducible grading of meningiomas. A number of their critical findings were adopted in the 2000 revision of the WHO classification of brain tumors. The meningioma grading scheme recently published in the 2007 revision is almost identical to that proposed by the Mayo group based on these two studies.

- **Defining Atypical Meningiomas**

The first study was a retrospective analysis of 581 patients with primary meningiomas.[32] In it, the investigators examined the correlation between numerous parameters, histological and otherwise, and progression-free survival. In defining the grading criteria, they included only patients with gross-total resections (463 patients).

The presence of mitotic figures numbering four or more per 10 hpf were highly predictive of recurrence and became one of the criteria for atypical meningioma. The second, independent criterion the researchers from the Mayo Clinic used was the presence of at least three of the following four parameters: "sheeting" (Fig. 5A), prominent nucleoli (Fig. 5B), hypercellularity, and the formation of small cells (Fig. 5C). Applying the proposed criteria, 81% of their meningiomas were classic and 15% atypical. The remaining 4% showed brain invasion and were dealt with separately. The 5-year recurrence rates were 12% for classic tumors and 41% for atypical tumors. Atypical tumors were associated with decreased overall length of survival; classic meningiomas were not.

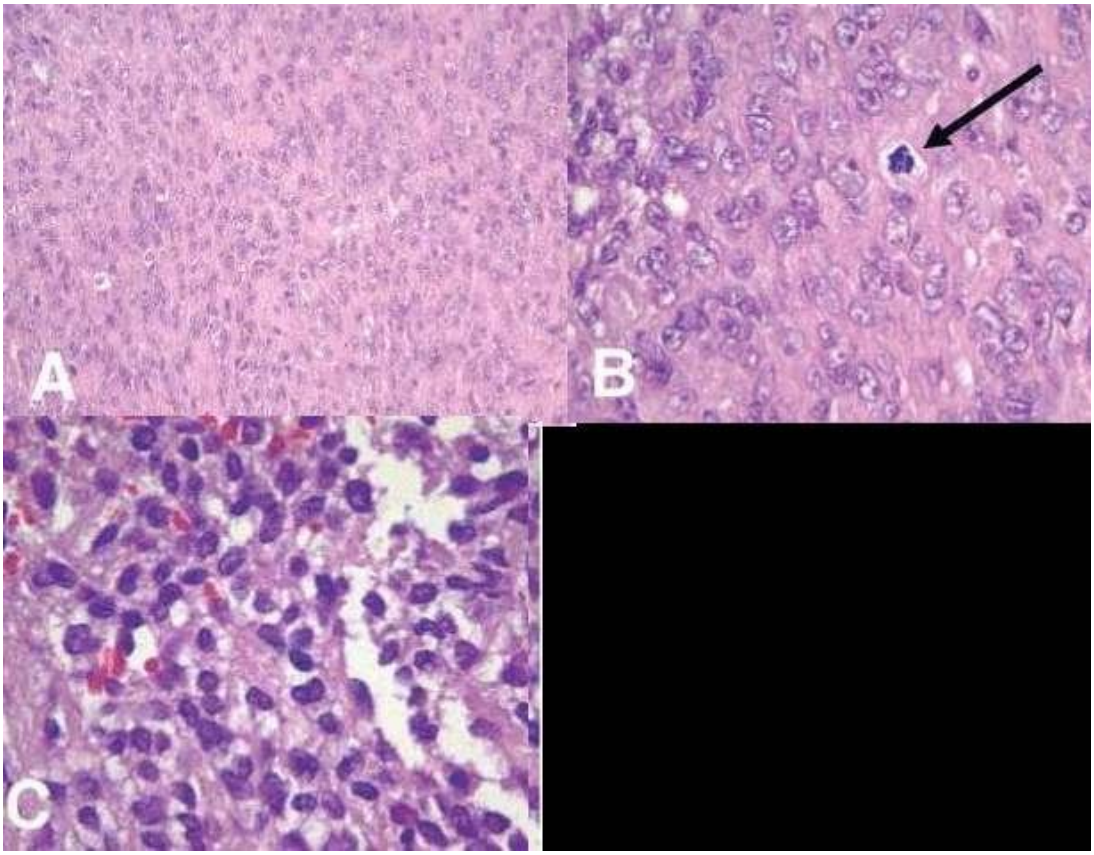

Figure 5. Photomicrographs demonstrating three of the histological criteria for atypia according to the Mayo Clinic grading scheme for meningiomas. A) patternless architecture or "sheeting;" B) prominent nucleoli (arrow indicates a mitotic figure); and C) formation of small cells. H & E, original magnification × 100 (A), × 400 (B and C).

- **Preliminary Findings Concerning Brain Invasion**

Most meningiomas have a "pushing" border with the brain and do not breach the pia. On the other hand, some meningiomas exhibit brain invasion characterized by an irregular border between the tumor and brain without intervening leptomeninges. The brain shows a gliotic response and there is often entrapment of islands of brain parenchyma within the tumor (Fig. 6). At the time of the Mayo Clinic studies, brain invasion was often equated with malignancy, irrespective of the other histopathological features of the tumor.[32]

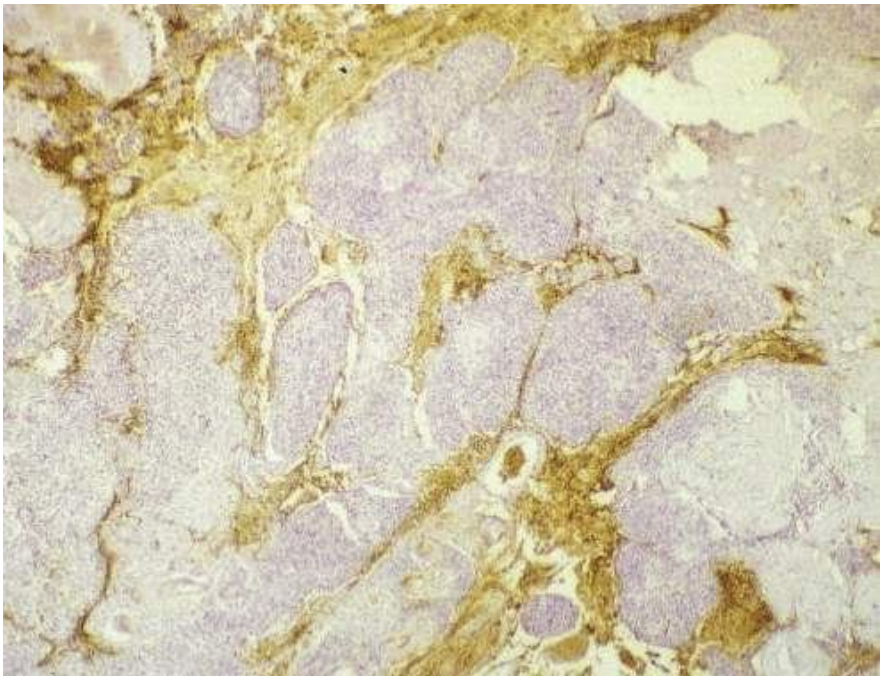

Figure 6. Immunohistochemical staining for glial fibrillary acidic protein demonstrating meningioma with brain invasion. The brain parenchyma stains positive (brown) for this protein, and the meningioma stains negative (purple), highlighting the extensive intermingling of the two tissues. Streptavidin–biotin, magnification × 200.

In the first Mayo Clinic study, brain invasion was a powerful predictor of shorter recurrence-free survival.[32] Of brain invasive tumors in their study, 43% had classic histological characteristics and 57% were atypical. The recurrence rate of invasive tumors, whether otherwise benign or atypical, was not statistically different from that of noninvasive atypical tumors. However, the authors felt that they could not draw definitive conclusions regarding brain invasion as a criterion for malignancy.

- **Defining Anaplastic Meningiomas and Revisiting Brain Invasion**

In the second study, the group from the Mayo Clinic investigated which histological features predict malignancy in meningiomas and again addressed the significance of brain invasion.[31] A diagnosis of malignant meningioma was identified in 116 patients based on one or more of the following criteria: brain invasion, frank anaplasia, and distant metastasis. The diagnosis of malignancy was based in most cases on the presence of brain invasion (86%). Extracranial metastasis was present in only 5% of cases.

On multivariate analysis, features associated with short survival were anaplasia and the presence of excessive mitoses (20 or more mitotic figures per 10 hpf). Anaplasia was defined as a loss of meningothelial features so that the tumor resembled a carcinoma, sarcoma, or melanoma, focally or diffusely. The median survival of patients with tumors considered malignant on the basis of anaplasia or excessive mitotic cells was 1.5 years. Extracranial metastases developed in only 11% of these tumors.

As in the first study, the median survival of patients with atypical and benign (classic) tumors that invaded brain did not differ significantly (10.4 and 14.9 years, respectively) Those that harbored anaplastic meningiomas had a significantly shorter median survival—1.4 years—which was essentially identical to that in patients with anaplastic tumors without brain invasion. The authors suggested that brain invasion should be another criterion for atypia (Grade II).

- **The WHO 2007 Grading Scheme for Meningiomas**

In 2000 the WHO published a revised grading scheme for meningiomas with criteria for atypia and anaplasia that were almost identical to those proposed in the two Mayo Clinic studies.[18] The only difference was that the WHO considered necrosis a feature of atypia (Fig. 7) and commented on the prognostic implications of brain invasion but did not include it as a criterion for atypia. The inclusion of brain invasion as a criterion for atypia is the only significant modification to the 2007 version of the WHO grading scheme (Table 4).[30]

Table 4. Summary of the 2007 WHO Grading Scheme for Meningiomas*

WHO Grade	Histological Subtype	Histological Features
I	meningothelial, fibroblastic, transitional, angiomatous, microcystic, secretory, lymphoplasmacytic metaplastic, psammomatous	does not fulfill criteria for Grade II or III
II (atypical)	chordoid, clear cell	4 or more mitotic cells per 10 hpf and/or 3 or more of the following: increased cellularity, small cells, necrosis, prominent nucleoli, sheeting, &/or brain invasion in an otherwise Grade I tumor
III (anaplastic)	papillary, rhabdoid	20 or more mitoses per 10 hpf and/or obviously malignant cytological characteristics such that tumor cell resembles carcinoma, sarcoma, or melanoma

**From Perry A, et al : Meningiomas, in Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. (eds): World Health Organization Classification of Tumours of the Central Nervous System, ed 4. Lyon: IARC, 2007, pp 164–172.*

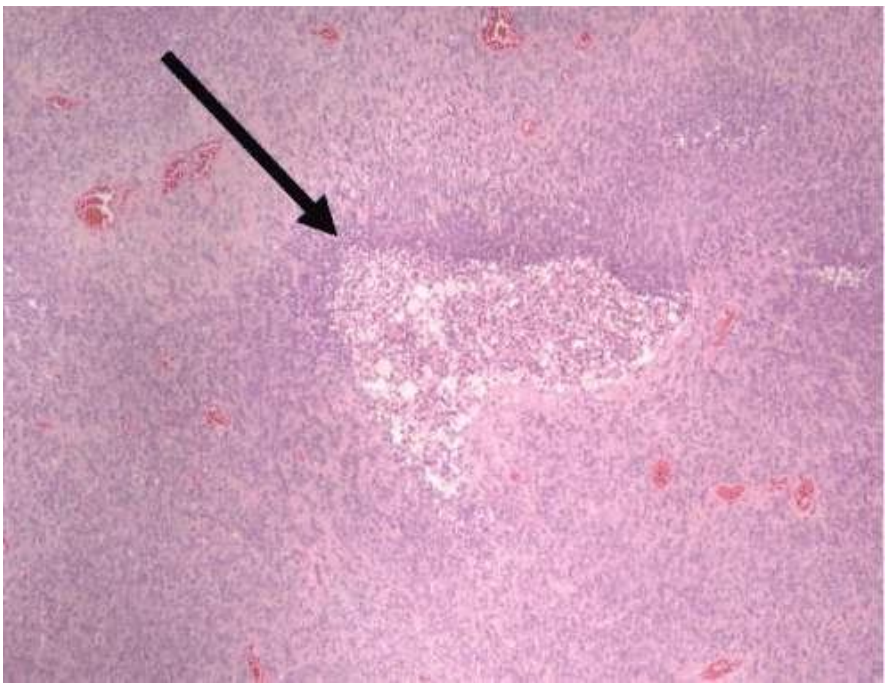

Figure 7. Photomicrograph demonstrating necrosis (arrow), a feature used in the 2000 WHO classification but not in the Mayo Clinic criteria for atypia. H & E, original magnification × 100.

- **Differential Diagnosis of Anaplastic Meningiomas**

Because a criterion for anaplastic meningioma is that it "resembles carcinoma, sarcoma, or melanoma," these lesions obviously enter the differential diagnosis in some Grade III meningiomas. The diagnosis of meningioma is supported by the following immunohistochemistry profile: at least focal membranous positivity for EMA, positivity for vimentin, negativity for cytokeratin, and weak or negative staining for S 100 protein. Most carcinomas will stain positive for cytokeratin and negative for vimentin. Most sarcomas will be positive for vimentin only or also show positivity for mesenchymal markers such as smooth muscle actin. Melanoma is usually positive for one or more melanoma markers such as HMB-45, S 100 (often strong and diffuse staining) and melan-A. In truly difficult cases, such as in tumors that are convincingly positive only for vimentin, ultrastructural examination may be helpful. Features typical of meningioma include interdigitating processes and intercellular junctions. However, in very poorly differentiated tumors, even ultrastructural evidence of meningothelial differentiation may be unconvincing and the presumptive diagnosis must be made on clinical grounds.

The tumor that most commonly has to be differentiated from an anaplastic meningioma is probably hemangiopericytoma. In contrast to anaplastic meningiomas (which only occasionally metastasize but have a median survival of under 2 years), 25 to 60% of hemangiopericytomas metastasize outside the central nervous system, and

median survivals range from 5 to 12 years, depending on the histo-pathological grade.[38]

Sometimes the classic "staghorn" vascular pattern of hemangiopericytoma is absent. In this case its patternless high cellularity and numerous mitotic cells can lead to confusion with anaplastic meningioma (Fig. 8). Generally the diagnosis can be made on the basis of negativity for EMA and abundant intercellular reticulin in the hemangiopericytoma. Ultrastructural analysis may confirm the diagnosis by showing basal lamina-like material that is present in hemangiopericytoma (but not meningioma) and the lack of meningothelial characteristics.

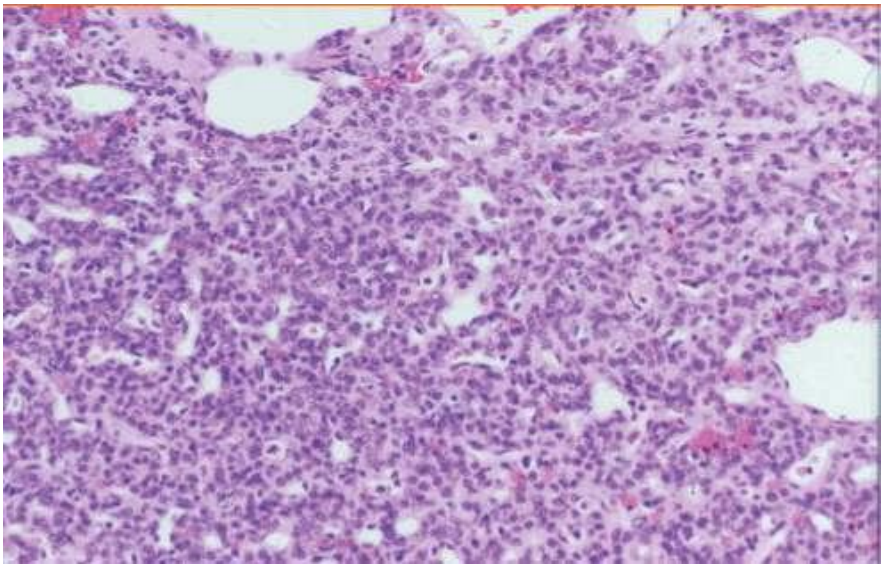

Figure 8. Photomicrograph of hemangiopericytoma, a primary dural sarcoma often included in the differential diagnosis of an-aplastic meningioma. This example shows vascular spaces that are vaguely "staghorn" in appearance. H & E, original magnification × 200.

Unfortunately, some hemangiopericytomas can show focal positivity for EMA, and the other differentiating features may be inconclusive. In such cases, a more extensive immunohistochemistry panel and/or genetic studies have been suggested.[38] Strong expression of CD99 (O13) and bcl-2 is highly specific for hemangiopericytoma in the differential diagnosis of anaplastic meningioma. Deletions of 1p32, 14q32, NF2, and 4.1B (18p11) are extremely common in anaplastic meningiomas but very rare in heman-giopericytoma.

- **Another Modification: Identification of Additional Aggressive Histological Variants of Meningioma**

The 1993 WHO classification of brain tumors recognized only one histological variant of meningioma that was considered a Grade II to III tumor: the papillary meningioma.[17] In their usual form, the other 11 recognized histological variants were considered benign, Grade I tumors. These are the meningothelial, transitional, fibroblastic, microcystic, secretory, metaplastic, psammomatous, lymphoplasmacyte-rich, angiomatous, clear cell, and chordoid variants (Fig. 9). However, in the revised classification, the clear cell and chordoid versions are now classified as Grade II (Table 4). In addition, a 13th variant, the rhabdoid meningioma, is now recognized and classified as Grade III, along with the papillary meningioma. These aggressive meningioma variants are very rare tumors, each constituting no more than 1 to 2% of meningiomas. As a consequence, the literature concerning them consists of case reports and a few small clinical series. Interestingly, these aggressive variants were much more common in a study of pediatric and NF2-associated meningiomas in which they comprised 25% of the tumors.[29]

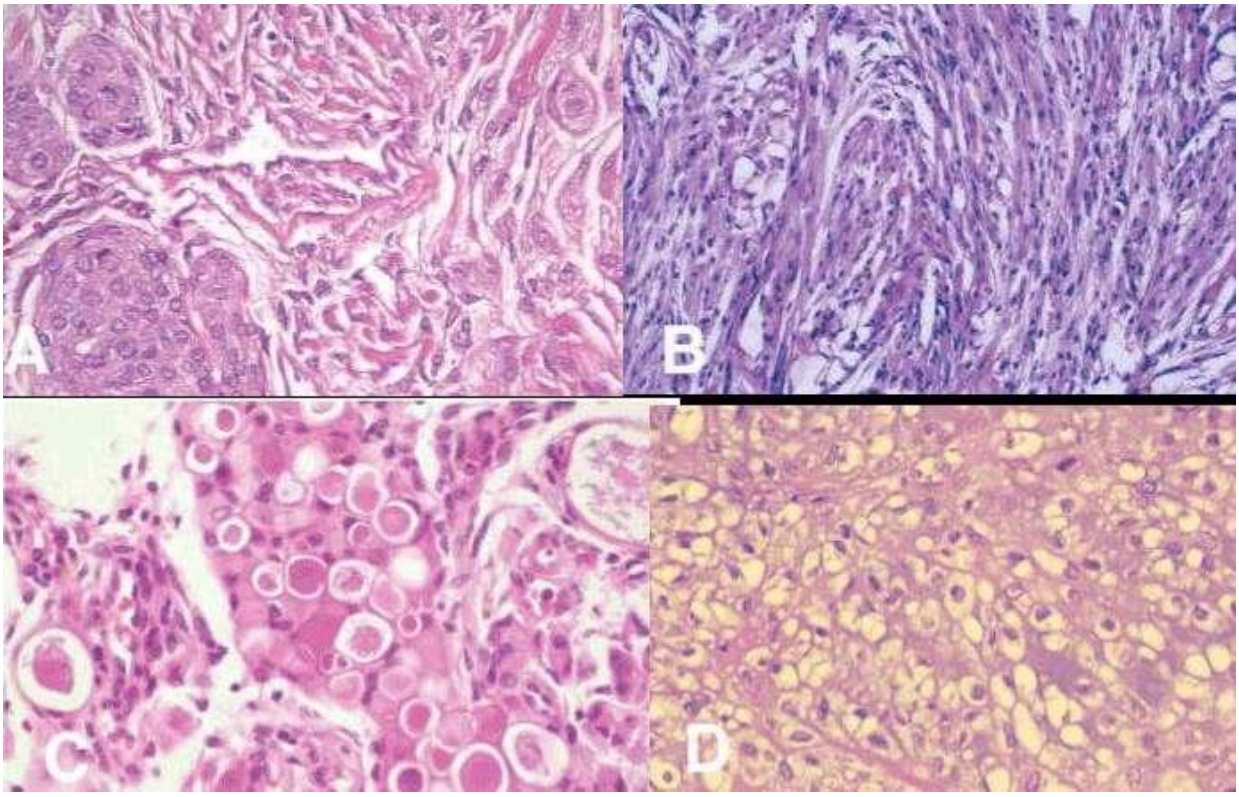

Figure 9. **Photomicrographs demonstrating characteristics of four examples of Grade I meningiomas. Transitional (A) and fibroblastic (B) are common histological variants of meningioma. Secretory (C) and metaplastic (D) are uncommon variants. H & E, original magnification × 400.**

- **Did Revision of the WHO Grading System in 2000 Change Anything?**

The Mayo Clinic scheme, which heavily influenced the 2000 WHO revision and the 2007 update, moved some otherwise benign or atypical tumors that invaded brain from the malignant to the atypical category. The proportion of tumors considered atypical in their report was approximately 18%, with a 5-year mortality rate of 21%. This represents a more than doubling in the proportion of meningiomas considered atypical.[18] Malignant or anaplastic tumors became rare and deadly, constituting only about 1% of all meningiomas with a 5-year mortality rate of 68%. [31]

The direction if not the magnitude of this change was confirmed in a study designed specifically to look at what effect, if any, adoption of the revised criteria might have.[47] Three hundred and fourteen meningiomas resected between 1994 and 2003 were studied. Lesions resected prior to 2001 were originally graded using the 1993 WHO criteria; those resected subsequently were graded according to the revised, 2000 WHO criteria. Brain invasion was not used in grading. The meningiomas were regraded without knowledge of the original results. Reassessment of meningiomas originally graded by the old criteria resulted in a change of grade in 13% of tumors and a 25% increase in Grade II tumors.

This study also reexamined meningiomas that had originally been graded according to the 2000 WHO criteria. Not every tumor received the same grade when reassessed using the same grading criteria, indicating that the revised scheme still does not give completely reproducible results. This is not surprising because, even though improved, the criteria are still somewhat vague and subjective.

- **Some Remaining Problems and Unresolved Issues in the Grading of Meningiomas**

  - **Invasion of Brain**

Questions still surround the issue of tumor invasion of brain. Grade I meningiomas can invade surrounding tissues such as bone and soft tissue; although this makes resection more difficult, it does not change the grade. Invasion of brain, on the other hand, results in a prognosis equivalent to that of an atypical meningioma, even if the tumor appears

otherwise benign. Is this simply because the tumor is inevitably left behind, or is there something intrinsically aggressive about these tumors? Indeed these tumors are more often higher grade, yet the genetic abnormalities seen in atypical and anaplastic meningiomas have not been observed in invasive, but otherwise histologically benign, tumors.[40,45] At this point, it is uncertain what causes invasiveness.

- **What Defines Malignancy in a Meningioma?**

In most types of tumors, distant metastasis is an indisputable indication of malignancy. This is not so clearly the case with meningiomas. Metastasis is a rare event in meningiomas, occurring in fewer than 1% of cases.[6] Local recurrence is the major cause of complications and death even in malignant meningiomas.[5] Metastasis often occurs only after local control has been lost.[11]

On the other hand, there have been examples of "benign metastasizing meningiomas" with bland, Grade I cytological characteristics and an indolent clinical course.[6,31] In some cases the metastatic foci were found at presentation, and thus could not be attributed to lymphovascular seeding due to surgical manipulation.[25,31] It has been suggested that the histological characteristics of the metastasis, rather than the fact that there is metastatic disease, may be more pertinent to the clinical outcome. Too little data are available to answer this question. Thus the relationship between histological grade, metastasis, and clinical outcome is not straightforward when considering meningiomas.

- **Potential Errors in Grading Due to Treatment Effects**

Preoperative embolization of meningiomas is used at some institutions to minimize intraoperative bleeding, but the fact that the tumor underwent embolization may not be communicated to the pathologist. Embolization induces some histological changes that may lead to overgrading the tumor, including macronucleoli, necrosis, and compensatory proliferation with increased numbers of mitotic figures.[24,26,28] In a 2001 study, Perry et al.[28] used the Mayo Clinic grading system described previously to grade 64 meningiomas that had been embolized. There were twice as many Grade II tumors (41%) as generally reported in series of nonembolized tumors; however, a comparison of grade and clinical outcome led them to conclude that more atypical tumors are selected for embolization, so their results were due to patient selection bias.

Communication between the neurosurgeon and neuro-pathologist regarding the use of embolization should reduce the risk of overgrading. Similarly, knowledge of the patient's history of radiation therapy will prevent undue concern over necrosis or cellular atypia.

- **Problems in Counting Mitotic Figures**

Counts of mitotic figures are central to the WHO system of grading meningiomas. The fact that this is a quantitative measure gives it a feeling of validity that is somewhat illusory. A number of factors can make it difficult to get an accurate count of mitotic figures. There is often considerable variation in the density of mitotic figures in different areas of a tumor. Mitotic figures are typically counted in the area of the tumor with the most mitotic figures, and there is an element of subjectivity in how this area is chosen by the pathologist. In a routine case, it is probably done by "eyeing it," because any other method is unacceptably time-consuming. In addition, it can be difficult to distinguish mitotic figures from apoptotic cells or from pyknotic nuclei.

Attempts have been made to improve the accuracy of mitotic figure counts in meningiomas by performing immunohistochemical staining specific for phosphorylated histone H3.[39] Histone H3 undergoes maximum phosphorylation during mitosis but remains unphosphorylated during apoptosis. In the study by Ribalta et al.,[39] the use of this modality resulted in an increased number of mitotic figures identified and an increase in grade for about 17% of tumors. The use of this stain has not become routine practice, however.

- **The Problem of Mixed Histological Characteristics**

It is not unusual for papillary, chordoid, rhabdoid, and, to a lesser extent, clear-cell meningiomas to manifest mixed histological characteristics. Such tumors show varying amounts of the papillary, chordoid, or rhabdoid pattern and the remainder of the tumor shows a more conventional pattern such as meningothelial. In most cases the latter will demonstrate evidence of aggressivity such as necrosis and frequent mitotic figures and would receive the same grade as the papillary, chordoid, or rhabdoid areas. In some cases, however, the areas with the conventional pattern are deemed lower grade. The prognostic significance of this is uncertain, particularly when the lower-grade, conventional areas dominate.

- **Adjunct Markers**

Numerous molecules have been investigated as possible predictors of prognosis with the goal of improving routine histological grading. These include various proliferation markers, cell cycle regulatory proteins, hormone receptors, and growth factors.[9,14,19-21,33,34,36,48] A good number of these have been shown to correlate with tumor grade, predict recurrence, or both, but large studies with consistent results are rare. Perhaps the use of tissue microarrays that allow rapid analysis of many specimens under identical staining conditions will speed the confirmation of positive findings.[20]

- **Proliferation Marker Ki 67 (MIB-1)**

Currently, the only adjunct marker commonly used in the evaluation of meningiomas is the proliferation marker Ki 67. The Ki 67 antigen is a nuclear protein present only during the active phases of the cell cycle (G1, S, G2, and M).[36] The MIB-1 antibody recognizes the Ki 67 antigen and can be used on paraffin sections. The MIB-1 LI is calculated as the percentage of tumor cell nuclei that stain positive out of the total number of tumor cell nuclei counted.

The use of MIB-1 LI as a prognostic indicator in meningiomas has been the subject of numerous studies. Most, but not all, studies have found significant differences between the MIB-1 labeling indices of benign, atypical, and ana-plastic meningiomas (Fig. 10).[3,22,23,42] However, the standard deviations are large, and there is overlap between grades, so the MIB-1 LI of a particular tumor must be interpreted cautiously.

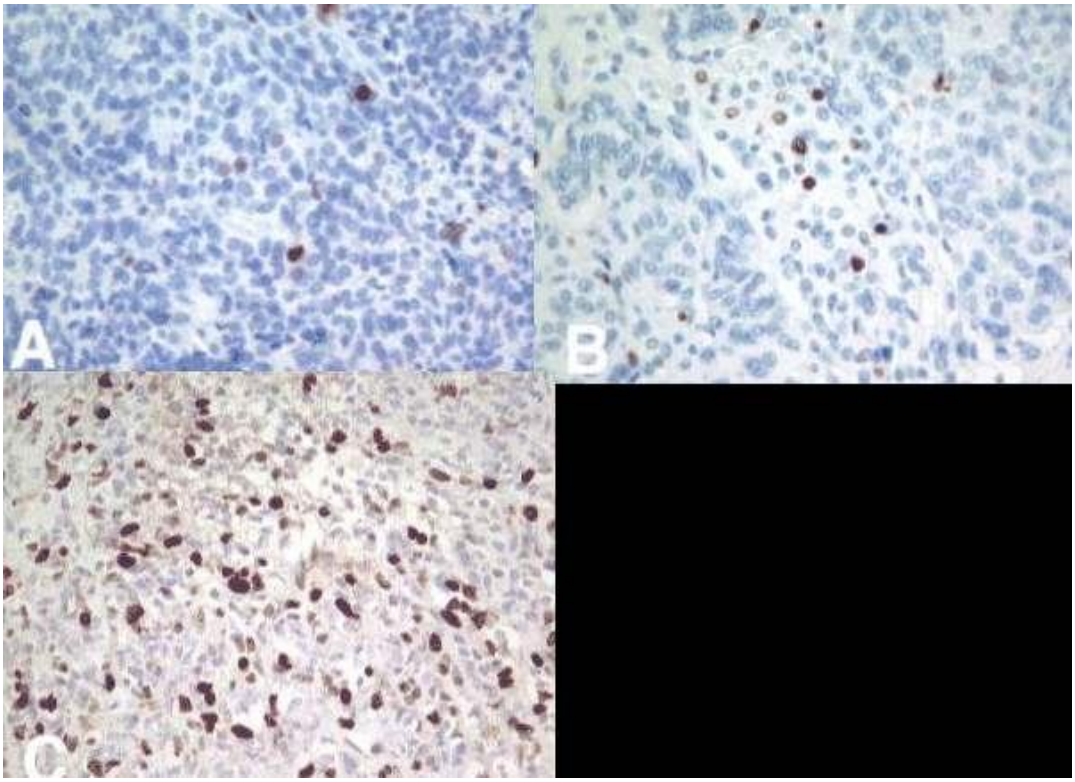

Figure 10. Photomicrographs showing Ki 67 (MIB-1) immunohistochemistry in different grades of meningioma. Grade I or benign meningioma (A), Grade II or atypical (B), Grade III or anaplastic (C). The differences in MIB-1 LIs between meningiomas of different grades are not always this obvious. Streptavidin–biotin, original magnification × 400.

Unfortunately, the usefulness of the MIB-1 LI is also limited by the fact that there is variability in results obtained at different laboratories due to differences in staining techniques, counting methods, and interpretation of results.[47] For example, different MIB-1 LIs are obtained depending on whether the count is performed in the area of tissue showing the densest labeling or in randomly chosen fields.[23] It has been suggested that the best use of MIB-1 LIs is as a tie-breaker in cases with borderline atypia with a cutoff value of 4.2%.[33] It has also been suggested that, given the variability between laboratories in technique, the use of a particular cutoff value should be validated in the user's own laboratory, or more practically, should only be used as a general guidline.[10,42] None of these authors suggested that MIB-1 LIs should replace grading meningiomas using routine histological methods.

As far as predicting decreased recurrence-free survival, most (but not all) studies show a significant correlation with MIB-1 LIs in either a multivariate analysis which adjusts for extent of resection, or when only tumors with a gross-total resection are considered.[3,10,13,33]

Authors of a study intended to address the problem of predicting behavior in Grade I tumors did not find a significant correlation between mean MIB-1 LI and recurrence-free survival in patients with benign tumors who underwent radical surgery.[42]

- **Progesterone Receptors**

It has long been postulated that activation of PRs may play a role in meningioma growth. Meningiomas are more common in women than men, and rapid growth and an exacerbation of symptoms have been observed during pregnancy.[48] Approximately 70% of meningiomas stain positive for PRs; there is no difference between the sexes in PR expression.[41] It is well established that higher grade tumors are more frequently PR negative.[19,41] Tumors that stain positive for PR appear to have lower proliferation indices and result in a better prognosis.[2,41] Progesterone receptor positivity is most commonly seen in the meningothelial variant of meningioma.[2,48] In some in vitro and animal studies, treatment with antiprogesterone agents has inhibited meningioma growth; however, this has not been convincingly duplicated in the clinical setting.[37,48]

Immunohistochemical positivity for estrogen receptors is rare in meningiomas. The expression of PR does not appear to be controlled by estrogen through the estrogen receptor[1] as it is in hormone-responsive tissue such as the breast. Positivity for estrogen receptors has been correlated with aggressive histological characteristics and chromosomal abnormalities; these same features are associated with PR negativity.[35]

- **Tumor Progression**

The existence of histological grades correlating with the behavior of meningiomas suggests that there is tumor progression. The assumption is that the underlying mechanism for progression is genetic and that it should generally be accompanied by changes in the histological characteristics of the tumor such that it becomes higher grade. The genetic abnormalities seen in meningiomas are numerous and thus support the idea of progression. Histological progression with tumor recurrence does occur, but in only a fraction of cases.

- **Genetic Abnormalities**

Loss of heterozygosity for markers on chromosome 22 in the region of the NF2 gene (22q12) is demonstrated in 40 to 70% of meningiomas.[43,45] In the majority of sporadic meningiomas with this loss, there are also mutations in the NF2 gene. These mutations occur in a similar proportion of Grade I, II, and III tumors, suggesting that inactivation of this gene is involved in initiation of tumor growth but not in its progression.[46] The frequency with which NF2 mutations are seen varies with histological subtype, and they are more common in tumors with a mesenchymal (fibroblastic) appearance.[15,46] Additional structural chromosomal abnormalities are rare in benign tumors, although there is abnormal expression of additional genes on 22q12 by means of several different mechanisms.[27,40]

In a study of correlations between recurrence-free survival and various clinical, histological, and genetic parameters, the loss of 1p was found to be the only independent predictor of recurrence in totally resected Grade I meningiomas. Decreased activity of nonspecific alkaline phosphatase, an enzyme marker for 1p loss, did not reach significance in multivariate testing, but was suggested as a fast and low-cost screening method for histologically benign but aggressive meningiomas.[12]

In addition to chromosome 22 abnormalities, atypical tumors characteristically show losses at 1p, 6q, 10q, 14q, and 18q.[45] Numerous other losses and also gains of genetic material have been described. Similar changes are seen in anaplastic tumors, but they also show losses on 9p and gains on 17q23. The loss on 9p contains genes that code for the cyclin-dependent kinase inhibitors and negative cell cycle regulators, p14(ARF), p15(INK4b), and p16(INK4a), all located at 9p21.[40] Patients with anaplastic meningiomas and deletion of 9p21 have a shorter survival.[27]

Activation of telomerase is a prominent feature of meningioma progression. The prevalence of telomerase in meningiomas varies in the literature but is seen in a minority of benign meningiomas and in almost 100% of anaplastic tumors.[4,16,44] A strong correlation between telomerase activity and a poor outcome has been demonstrated.[16]

- **Histological Progression**

When meningiomas recur, progression to a higher histological grade is relatively uncommon.[5,11,22,32] When this does occur, the change is almost always by only one grade, even with multiple recurrences. Additionally, the histological grade of the recurrence is sometimes lower than that of the original. These two observations suggest that sampling issues and/or inter- or intraobserver variability in grading may contribute in some instances to changes in tumor grade in cases of recurrence.

- **Abbreviation Notes**

EMA = epithelial membrane antigen; hpf = high-power field; LI = labeling index; NF2 = neurofibromatosis Type 2; PR = progesterone receptor; WHO = World Health Organization.

SUMMARY

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Our ability to identify meningiomas that will behave aggressively is limited. The WHO grading scheme published in 2000 represented a significant improvement over prior approaches to predicting meningioma behavior based on features seen on routine histological studies and is largely unaltered 7 years later. However, the grading scheme is still plagued by subjectivity and does not address the problem of the benign-appearing tumors that recur relentlessly and ultimately disable or kill the patient. Identification of such tumors at initial resection is highly desirable as a guide to subsequent therapy before the tumor declares its nature by recurring. Numerous molecules, most notably the proliferation-associated antigen Ki 67 (MIB-1), have been investigated for their potential to improve on the information provided by the grading system. So far the utility of this type of study has been as a supplement to routine grading rather than as a substitute. Genetic profiles of individual tumors may someday allow improved prediction of their behavior.

- **Addendum**

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